**[0010]** In view of the need for further cancer therapies, this disclosure provides methods of treating and diagnosing cancer related to PARN expression and activity that effects oncogene expression.

## SUMMARY OF INVENTION

**[0011]** The present inventors hypothesized that PARN deficiency affects the stability of miRNAs in human cells, which could explain the severe phenotype of PARN deficiency in DC patients. They have now surprisingly shown that in HeLa cells, PARN affects the levels of several miRNAs both positively and negatively. Further, they have shown that PARN protects miRNAs from degradation by removing adenosines from their 3' ends that are added by the poly(A) polymerase PAPD5. In the absence of PARN, 3' end adenylation leads to recruitment of the cytoplasmic exonucleases DIS3L or DIS3L2, which leads to miRNA degradation. They have also found that several miRNAs that are decreased in PARN depleted cells target the p53 mRNA, and that PARN knockdown leads to a very strong upregulation of p53 protein levels in HeLa cells, with or without DNA damage. They have also shown that PARN knockdown sensitizes HeLa cells to chemotherapeutic agents, leading to cell cycle arrest and apoptosis. These findings explain why PARN mutations lead to a severe phenotype of DC in patients, because chronic upregulation of p53 signaling could negatively affect cell growth and development in these patients at a very young age. Additionally, the use of PARN inhibitors combined with chemotherapy could be a therapeutic strategy to treat a subset of cancers that are caused by repressed wild-type p53 protein.

**[0012]** Thus, this disclosure provides methods of reducing the severity of one or more symptom(s) of cancer in a patient, and/or identifying a cancer patient that may selectively benefit from the administration of one or more PARN inhibitor(s) or the administration of the combination of one or more PARN inhibitor(s) and one or more chemotherapeutic agent(s), and/or diagnosing a chemotherapy-resistant or chemotherapy-sensitive cancer by measuring one or more feature(s) in cancer cell(s) from a patient selected from levels of poly(A)-specific ribonuclease (PARN), levels of phosphorylated PARN, and determining from the measurements whether the cancer cell(s) in the patient has one or more feature(s) of an activated PARN and/or an inactivated p53 signaling pathway relative to these features in a control sample; and administering to a patient determined to have a cancer cell having one or more the feature(s) of an activated PARN and/or an activated p53 signaling pathway one or more P53 inhibitor(s) for a time and in an amount sufficient to reduce the severity of one or more symptom(s) of cancer in the patient.

**[0013]** Additional embodiments of the above methods include measuring one or more feature(s) in the cancer cell(s) selected from tumor protein-53 (p53) mRNA or protein levels, and cyclin-dependent kinase inhibitor 1 (p21) expression or activity, and determining from these measurements whether the cancer cell(s) in the patient have one or more feature(s) of an inactivated p53 signaling pathway selected from decreased p53 mRNA or protein levels, expression of a mutant or truncated p53 with decreased expression or activity, and decreased p21 expression or activity, relative to these features in a control sample. These methods may further include administering to a patient determined to have a cancer cell having one or more the feature(s) of an inactivated p53 signaling pathway a PARN inhibitor for a time and in an amount sufficient to reduce the severity of one or more symptom(s) of cancer in the patient. Further embodiments of any of the above methods further comprise the step of administering one or more chemotherapeutic agent(s) (e.g., a chemotherapeutic agent that induces DNA damage) to the patient.

**[0014]** In any of the above methods, the control sample in step (ii) may be a non-cancerous cell or a cell untreated with a genotoxic agent and/or the control sample in step (v) is a non-cancerous cell.

**[0015]** In any of the above methods, the PARN inhibitor may be a small molecule, or an siRNA molecule or a nucleobase oligomer containing a sequence complementary to at least 10 consecutive nucleotides of a nucleic acid sequence encoding a PARN protein, or a peptide that may be covalently-linked to a moiety capable of translocating across a biological membrane (e.g., a moiety that contains a penetrating peptide or a TAT peptide).

**[0016]** In any of the above methods, the patient may have previously received at least one dosage of a chemotherapeutic agent. In additional embodiments of the above methods, the control sample is a cancer cell or non-cancerous cell treated with a genotoxic agent and/or the control sample is a non-cancerous cell.

**[0017]** This disclosure further provides methods of treating a cancer patient diagnosed as having a chemotherapy-resistant cancer by any of the above methods, requiring the step of administering to the patient one or more PARN inhibitor(s). These methods may further include administering one or more chemotherapeutic agent(s) (e.g., a chemotherapeutic agent that induces DNA damage) to the patient.

**[0018]** In any of the above methods, the chemotherapeutic agent may be selected from the group of: alemtuzumab, altretamine, aminoglutethimide, amsacrine, anastrozole, azacitidine, bleomycin, bicalutamide, busulfan, capecitabine, carboplatin, carmustine, celecoxib, chlorambucil, 2-chlorodeoxyadenosine, cisplatin, colchicine, cyclophosphamide, cytarabine, cytoxan, dacarbazine, dactinomycin, daunorubicin, docetaxel, doxorubicin, epirubicin, estramustine phosphate, etodolac, etoposide, exemestane, floxuridine, fludarabine, 5-fluorouracil, flutamide, formestane, gemcitabine, gentuzumab, goserelin, hexamethylmelamine, hydroxyurea, hypericin, ifosfamide, imatinib, interferon, irinotecan, letrozole, leuporelin, lomustine, mechlorethamine, melphalen, mercaptopurine, 6-mercaptopurine, methotrexate, mitomycin, mitotane, mitoxantrone, nilutamide, nocodazole, paclitaxel, pentostatin, procarbazine, raltitrexed, rituximab, rofecoxib, streptozocin, tamoxifen, temozolomide, teniposide, 6-thioguanine, topotecan, toremofine, trastuzumab, vinblastine, vincristine, vindesine, and vinorelbine.

**[0019]** In any of these methods, the cancer may be selected from acoustic neuroma, acute leukemia, acute lymphocytic leukemia, acute monocytic leukemia, acute myeloblastic leukemia, acute myelocytic leukemia, acute myelomonocytic leukemia, acute promyelocytic leukemia, acute erythroleukemia, adenocarcinoma, angiosarcoma, astrocytoma, basal cell carcinoma, bile duct carcinoma, bladder carcinoma, brain cancer, breast cancer, bronchogenic carcinoma, cervical cancer, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic leukemia, colon cancer, colon carcinoma, craniopharyngioma, cystadenocarcinoma, embryonal